

# Package ‘glmSparseNet’

May 16, 2024

**Type** Package

**Title** Network Centrality Metrics for Elastic-Net Regularized Models

**Version** 1.22.0

**Description** glmSparseNet is an R-package that generalizes sparse regression models when the features (e.g. genes) have a graph structure (e.g. protein-protein interactions), by including network-based regularizers. glmSparseNet uses the glmnet R-package, by including centrality measures of the network as penalty weights in the regularization. The current version implements regularization based on node degree, i.e. the strength and/or number of its associated edges, either by promoting hubs in the solution or orphan genes in the solution. All the glmnet distribution families are supported, namely ``gaussian``, ``poisson``, ``binomial``, ``multinomial``, ``cox``, and ``mgaussian``.

**License** GPL-3

**URL** <https://www.github.com/sysbiomed/glmSparseNet>

**BugReports** <https://www.github.com/sysbiomed/glmSparseNet/issues>

**Depends** R (>= 4.3.0)

**Imports** biomaRt, checkmate, dplyr, forcats, futile.logger, ggplot2, glue, httr, lifecycle, methods, parallel, readr, rlang, glmnet, Matrix, MultiAssayExperiment, SummarizedExperiment, survminer, TCGAutils, utils

**Suggests** BiocStyle, curatedTCGADData, knitr, magrittr, reshape2, pROC, rmarkdown, survival, testthat, VennDiagram, withr

**VignetteBuilder** knitr

**RdMacros** lifecycle

**biocViews** Software, StatisticalMethod, DimensionReduction, Regression, Classification, Survival, Network, GraphAndNetwork

**Encoding** UTF-8

**Language** en-US

**LazyData** false

**NeedsCompilation** no

**Roxygen** list(markdown = TRUE)

**RoxygenNote** 7.3.1

**git\_url** <https://git.bioconductor.org/packages/glmSparseNet>

**git\_branch** RELEASE\_3\_19

**git\_last\_commit** 7b32a0f

**git\_last\_commit\_date** 2024-04-30

**Repository** Bioconductor 3.19

**Date/Publication** 2024-05-16

**Author** André Veríssimo [aut, cre] (<<https://orcid.org/0000-0002-2212-339X>>),  
 Susana Vinga [aut],  
 Eunice Carrasquinha [ctb],  
 Marta Lopes [ctb]

**Maintainer** André Veríssimo <[andre.verissimo@tecnico.ulisboa.pt](mailto:andre.verissimo@tecnico.ulisboa.pt)>

## Contents

glmSparseNet-package . . . . .	3
.baseDir . . . . .	4
.biomartLoad . . . . .	4
.buildFunctionDigest . . . . .	5
.cacheCompression . . . . .	6
.calcPenalty . . . . .	7
.calculateResult . . . . .	7
.combinedScore . . . . .	8
.createDirectoryForCache . . . . .	9
.curlWorkaround . . . . .	9
.degreeGeneric . . . . .	10
.digestCache . . . . .	11
.glmSparseNetPrivate . . . . .	12
.networkGenericParallel . . . . .	13
.networkWorker . . . . .	14
.runCache . . . . .	14
.saveRunCache . . . . .	16
.showMessage . . . . .	16
.tempdirCache . . . . .	17
.writeReadme . . . . .	17
balancedCvFolds . . . . .	18
buildLambda . . . . .	18
buildStringNetwork . . . . .	20
cv.glmDegree . . . . .	21
degreeCor . . . . .	24
degreeCov . . . . .	25
downloadFileLocal . . . . .	27

ensemblGeneNames . . . . .	27
geneNames . . . . .	28
glmSparseNet . . . . .	29
hallmarks . . . . .	32
heuristicScale . . . . .	33
hubHeuristic . . . . .	34
myColors . . . . .	34
mySymbols . . . . .	35
networkCorParallel . . . . .	35
networkCovParallel . . . . .	36
networkOptions . . . . .	37
orphanHeuristic . . . . .	38
protein2EnsemblGeneNames . . . . .	39
separate2GroupsCox . . . . .	40
string.network.700.cache . . . . .	42
stringDBhomoSapiens . . . . .	42
<b>Index</b>	<b>44</b>

---

glmSparseNet-package    *glmSparseNet: Network Centrality Metrics for Elastic-Net Regularized Models*

---

## Description

glmSparseNet is an R-package that generalizes sparse regression models when the features (e.g. genes) have a graph structure (e.g. protein-protein interactions), by including network-based regularizers. glmSparseNet uses the glmnet R-package, by including centrality measures of the network as penalty weights in the regularization. The current version implements regularization based on node degree, i.e. the strength and/or number of its associated edges, either by promoting hubs in the solution or orphan genes in the solution. All the glmnet distribution families are supported, namely "gaussian", "poisson", "binomial", "multinomial", "cox", and "mgaussian".

## Author(s)

**Maintainer:** André Veríssimo <andre.verissimo@tecnico.ulisboa.pt> ([ORCID](#))

Authors:

- Susana Vinga <susanavinga@tecnico.ulisboa.pt>

Other contributors:

- Eunice Carrasquinha <eunice.trigueirao@tecnico.ulisboa.pt> [contributor]
- Marta Lopes <marta.lopes@tecnico.ulisboa.pt> [contributor]

**See Also**

Useful links:

- <https://www.github.com/sysbiomed/glmSparseNet>
- Report bugs at <https://www.github.com/sysbiomed/glmSparseNet/issues>

---

<code>.baseDir</code>	<i>Change base dir for '.runCache</i>
-----------------------	---------------------------------------

---

**Description**

Change base dir for '.runCache

**Usage**

```
.baseDir(path = NULL)
```

**Arguments**

path                    to base directory where cache is saved

**Value**

the new path

**Examples**

```
glmSparseNet:::.baseDir("/tmp/cache")
```

---

<code>.biomartLoad</code>	<i>Common call to biomaRt to avoid repetitive code</i>
---------------------------	--

---

**Description**

Common call to biomaRt to avoid repetitive code

**Usage**

```
.biomartLoad(attributes, filters, values, useCache, verbose)
```

### Arguments

attributes	Attributes you want to retrieve. A possible list of attributes can be retrieved using the function <code>biomaRt::listAttributes</code> .
filters	Filters (one or more) that should be used in the query. A possible list of filters can be retrieved using the function <code>biomaRt::listFilters</code> .
values	Values of the filter, e.g. vector of affy IDs. If multiple filters are specified then the argument should be a list of vectors of which the position of each vector corresponds to the position of the filters in the filters argument
useCache	Boolean indicating if <code>biomaRt</code> cache should be used
verbose	When using <code>biomaRt</code> in webservice mode and setting <code>verbose</code> to <code>TRUE</code> , the XML query to the webservice will be printed.

### Value

data.frame with attributes as columns and values translated to them

### See Also

`geneNames`  
`ensemblGeneNames`  
`protein2EnsemblGeneNames`  
`biomaRt::getBM()`  
`biomaRt::useEnsembl()`

### Examples

```
glmSparseNet:::biomartLoad(  
  attributes = c("external_gene_name", "ensembl_gene_id"),  
  filters = "external_gene_name",  
  values = c("MOB1A", "RFLNB", "SPIC", "TP53"),  
  useCache = TRUE,  
  verbose = FALSE  
)
```

---

`.buildFunctionDigest` *Build digest of function from the actual code*

---

### Description

Build digest of function from the actual code

### Usage

```
.buildFunctionDigest(fun)
```

**Arguments**

fun            function call name

**Value**

a digest

**Examples**

```
glmSparseNet:::buildFunctionDigest(sum)
glmSparseNet:::buildFunctionDigest(c)
```

---

*.cacheCompression*      *Change cache.compression for run\_cache*

---

**Description**

Change cache.compression for run\_cache

**Usage**

```
.cacheCompression(compression = NULL)
```

**Arguments**

compression    see compression parameter in save function

**Value**

the new compression

**Examples**

```
glmSparseNet:::cacheCompression("bzip2")
```

---

.calcPenalty                    *Calculate penalty based on data*

---

**Description**

Internal method to calculate the network using data-dependant methods

**Usage**

```
.calcPenalty(xdata, penaltyType, options = networkOptions())
```

**Arguments**

xdata	input data
penaltyType	which method to use
options	options to be used

**Value**

vector with penalty weights

**Examples**

```
xdata <- matrix(rnorm(1000), ncol = 200)
glmSparseNet:::calcPenalty(xdata, "none")
glmSparseNet:::calcPenalty(
  xdata, "correlation",
  networkOptions(cutoff = .6)
)
glmSparseNet:::calcPenalty(xdata, "correlation")
glmSparseNet:::calcPenalty(
  xdata, "covariance",
  networkOptions(cutoff = .6)
)
glmSparseNet:::calcPenalty(xdata, "covariance")
```

---

.calculateResult                *Calculate/load result and save if necessary*

---

**Description**

This is where the actual work is done

**Usage**

```
.calculateResult(path, compression, forceRecalc, showMessage, fun, ...)
```

**Arguments**

path	path to save cache
compression	compression used in save
forceRecalc	force to recalculate cache
showMessage	boolean to show messages
fun	function to be called
...	arguments to said function ,

**Value**

result of fun(...)

**Examples**

```
glmSparseNet:::.calculateResult(
  file.path(tempdir(), "calculate_result.Rdata"),
  "gzip",
  FALSE,
  TRUE,
  sum,
  1, 2, 3
)
```

---

.combinedScore

*Calculate combined score for STRINGdb interactions*

---

**Description**

Please note that all the interactions have duplicates as it's a two way interaction (score(ProteinA-Protein) == score(ProteinB, PorteinA))

**Usage**

```
.combinedScore(allInteractions, scoreThreshold, removeText)
```

**Arguments**

allInteractions	table with score of all interactions
scoreThreshold	threshold to keep interactions
removeText	remove text-based interactions

**Details**

To better understand how the score is calculated, please see: <https://string-db.org/help/faq/#how-are-the-scores-computed>

**Value**

table with combined score

---

`.createDirectoryForCache`  
*Create directories for cache*

---

**Description**

Create directories for cache

**Usage**

```
.createDirectoryForCache(baseDir, parentPath)
```

**Arguments**

<code>baseDir</code>	tentative base dir to create.
<code>parentPath</code>	first 4 characters of digest that will become parent directory for the actual cache file (this reduces number of files per folder)

**Value**

a list of updated `baseDir` and `parentDir`

**Examples**

```
glmSparseNet:::createDirectoryForCache(tempdir(), "abcd")  
glmSparseNet:::createDirectoryForCache(  
  file.path(getwd(), "run-cache"), "abcd"  
)
```

---

`.curlWorkaround`      *Workaround for bug with curl when fetching specific ensembl mirror*

---

**Description**

Should be solved in issue #39, will test to remove it.

**Usage**

```
.curlWorkaround(expr)
```

**Arguments**

expr                    expression

**Value**

result of expression

**Examples**

```
glmSparseNet:::curlWorkaround({
  biomaRt::useEnsembl(
    biomart = "genes",
    dataset = "hsapiens_gene_ensembl"
  )
})
```

---

.degreeGeneric

*Generic function to calculate degree based on data*

---

**Description**

The assumption to use this function is that the network represented by a matrix is symmetric and without any connection the node and itself.

**Usage**

```
.degreeGeneric(
  fun = stats::cor,
  funPrefix = "operator",
  xdata,
  cutoff = 0,
  considerUnweighted = FALSE,
  chunks = 1000,
  forceRecalcDegree = FALSE,
  forceRecalcNetwork = FALSE,
  nCores = 1,
  ...
)
```

**Arguments**

fun                    function that will calculate the edge weight between 2 nodes

funPrefix            used to store low-level information on network as it can become to large to be stored in memory

xdata                calculate correlation matrix on each column

cutoff                positive value that determines a cutoff value

`considerUnweighted`      consider all edges as 1 if they are greater than 0

`chunks`                  calculate function at batches of this value (default is 1000)

`forceRecalcDegree`      force recalculation of penalty weights (but not the network), instead of going to cache

`forceRecalcNetwork`    force recalculation of network and penalty weights, instead of going to cache

`nCores`                  number of cores to be used

`...`                    extra parameters for fun

**Value**

a vector of the degrees

---

<code>.digestCache</code>	<i>Default digest method</i>
---------------------------	------------------------------

---

**Description**

Sets a default caching algorithm to use with `.runCache`

**Usage**

`.digestCache(val)`

**Arguments**

`val`                    object to calculate hash over

**Value**

a hash of the sha256

**Examples**

```
glmSparseNet:::digestCache(c(1, 2, 3, 4, 5))  
glmSparseNet:::digestCache("some example")
```

---

*.glmSparseNetPrivate*    *Calculate GLM model with network-based regularization*

---

### **Description**

Calculate GLM model with network-based regularization

### **Usage**

```
.glmSparseNetPrivate(  
  fun,  
  xdata,  
  ydata,  
  network,  
  experiment = NULL,  
  options = networkOptions(),  
  ...  
)
```

### **Arguments**

<code>fun</code>	function to be called ( <code>glmnet</code> or <code>cv.glmnet</code> )
<code>xdata</code>	input data, can be a matrix or <code>MultiAssayExperiment</code>
<code>ydata</code>	response data compatible with <code>glmnet</code>
<code>network</code>	type of network, see below
<code>experiment</code>	when <code>xdata</code> is a <code>MultiAssayExperiment</code> object this parameter is required
<code>options</code>	options to calculate network
<code>...</code>	parameters that <code>glmnet</code> accepts

### **Value**

an object just as `glmnet` network parameter accepts:

- string to calculate network based on data (correlation, covariance)
- matrix representing the network
- vector with already calculated penalty weights (can also be used directly with `glmnet`)

---

.networkGenericParallel

*Calculate the upper triu of the matrix*

---

### **Description**

Calculate the upper triu of the matrix

### **Usage**

```
.networkGenericParallel(  
  fun,  
  funPrefix,  
  xdata,  
  buildOutput = "matrix",  
  nCores = 1,  
  forceRecalcNetwork = FALSE,  
  showMessage = FALSE,  
  ...  
)
```

### **Arguments**

fun	function that will calculate the edge weight between 2 nodes
funPrefix	used to store low-level information on network as it can become to large to be stored in memory
xdata	base data to calculate network
buildOutput	if output returns a 'matrix', 'vector' of the upper triu without the diagonal or NULL with any other argument
nCores	number of cores to be used
forceRecalcNetwork	force recalculation, instead of going to cache
showMessage	shows cache operation messages
...	extra parameters for fun

### **Value**

depends on buildOutput parameter

---

<code>.networkWorker</code>	<i>Worker to calculate edge weight for each pair of ixI node and following</i>
-----------------------------	--

---

**Description**

Note that it assumes it does not calculate for index below and equal to ixI

**Usage**

```
.networkWorker(fun, xdata, ixI, ...)
```

**Arguments**

<code>fun</code>	function to be used, can be cor, cov or any other defined function
<code>xdata</code>	original data to calculate the function over
<code>ixI</code>	starting index, this can be used to save ony upper triu
<code>...</code>	extra parameters for fun

**Value**

a vector with size `ncol(xdata) - ixI`

---

<code>.runCache</code>	<i>Run function and save cache</i>
------------------------	------------------------------------

---

**Description**

This method saves the function that's being called

**Usage**

```
.runCache(
  fun,
  ...,
  seed = NULL,
  baseDir = NULL,
  cachePrefix = "generic_cache",
  cacheDigest = list(),
  showMessage = NULL,
  forceRecalc = FALSE,
  addToHash = NULL
)

## S4 method for signature 'function'
```

```
.runCache(  
  fun,  
  ...,  
  seed = NULL,  
  baseDir = NULL,  
  cachePrefix = "generic_cache",  
  cacheDigest = list(),  
  showMessage = NULL,  
  forceRecalc = FALSE,  
  addToHash = NULL  
)
```

### Arguments

<code>fun</code>	function call name
<code>...</code>	parameters for function call
<code>seed</code>	when function call is random, this allows to set seed beforehand
<code>baseDir</code>	directory where data is stored
<code>cachePrefix</code>	prefix for file name to be generated from parameters (...)
<code>cacheDigest</code>	cache of the digest for one or more of the parameters
<code>showMessage</code>	show message that data is being retrieved from cache
<code>forceRecalc</code>	force the recalculation of the values
<code>addToHash</code>	something to add to the filename generation

### Value

the result of `fun(...)`

### Functions

- `.runCache(`function`)`: accepts function as first argument and save cache

### Examples

```
# [optional] save cache in a temporary directory  
#  
glmSparseNet:::baseDir(tempdir())  
glmSparseNet:::runCache(c, 1, 2, 3, 4)  
#  
# next three should use the same cache  
# note, the middle call should be a little faster as digest is not  
# calculated  
# for the first argument  
glmSparseNet:::runCache(c, 1, 2, 3, 4)  
glmSparseNet:::runCache(c, a = 1, 2, c = 3, 4)  
  
# Using a local folder  
# glmSparseNet:::runCache(c, 1, 2, 3, 4, baseDir = "runcache")
```

---

`.saveRunCache`      *Saving the cache*

---

**Description**

Saving the cache

**Usage**

```
.saveRunCache(result, path, compression, showMessage)
```

**Arguments**

<code>result</code>	main result to save
<code>path</code>	path to the file to save
<code>compression</code>	compression method to be used
<code>showMessage</code>	TRUE to show messages, FALSE otherwise

**Value**

result of save operation

**Examples**

```
glmSparseNet:::saveRunCache(
  35, file.path(tempdir(), "save_run_cache.Rdata"), FALSE, TRUE
)
```

---

`.showMessage`      *Show messages option in .runCache*

---

**Description**

Show messages option in .runCache

**Usage**

```
.showMessage(showMessage = NULL)
```

**Arguments**

<code>showMessage</code>	boolean indicating to show messages or not
--------------------------	--

**Value**

the show.message option

**Examples**

```
glmSparseNet:::showMessage(FALSE)
```

---

<code>.tempdirCache</code>	<i>Temporary directory for runCache</i>
----------------------------	---

---

**Description**

Temporary directory for runCache

**Usage**

```
.tempdirCache()
```

**Value**

a path to a temporary directory used by runCache

---

<code>.writeReadme</code>	<i>Write a file in run-cache directory to explain the origin</i>
---------------------------	--

---

**Description**

Write a file in run-cache directory to explain the origin

**Usage**

```
.writeReadme(baseDir)
```

**Arguments**

`baseDir`            directory where to build this file

**Value**

the path to the file it has written

**Examples**

```
glmSparseNet:::writeReadme(tempdir())
```

---

balancedCvFolds	<i>Create balanced folds for cross validation using stratified sampling</i>
-----------------	---

---

### Description

Create balanced folds for cross validation using stratified sampling

### Usage

```
balancedCvFolds(..., nfolds = 10)

# deprecated, please use balancedCvFolds()
balanced.cv.folds(..., nfolds = 10)
```

### Arguments

...	vectors representing data
nfolds	number of folds to be created

### Value

list with given input, nfolds and result. The result is a list matching the input with foldid attributed to each position.

### Examples

```
balancedCvFolds(seq(10), seq(11, 15), nfolds = 2)

# will give a warning
balancedCvFolds(seq(10), seq(11, 13), nfolds = 10)

balancedCvFolds(seq(100), seq(101, 133), nfolds = 10)
```

---

buildLambda	<i>Auxiliary function to generate suitable lambda parameters</i>
-------------	--

---

### Description

Auxiliary function to generate suitable lambda parameters

**Usage**

```
buildLambda(  
  lambdaLargest = NULL,  
  xdata = NULL,  
  ydata = NULL,  
  family = NULL,  
  ordersOfMagnitudeSmaller = 3,  
  lambdaPerOrderMagnitude = 150,  
  lambda.largest = deprecated(),  
  orders.of.magnitude.smaller = deprecated(),  
  lambda.per.order.magnitude = deprecated()  
)
```

**Arguments**

lambdaLargest    numeric value for largest number of lambda to consider (usually with a target of 1 selected variable)

xdata            X parameter for glmnet function

ydata            Y parameter for glmnet function

family           family parameter to glmnet function

ordersOfMagnitudeSmaller  
                  minimum value for lambda ( $\text{lambda.largest} / 10^{\text{orders.of.magnitude.smaller}}$ )

lambdaPerOrderMagnitude  
                  how many lambdas to create for each order of magnitude

lambda.largest   **[Deprecated]**

orders.of.magnitude.smaller  
                  **[Deprecated]**

lambda.per.order.magnitude  
                  **[Deprecated]**

**Value**

a numeric vector with suitable lambdas

**Examples**

```
buildLambda(5.4)
```

---

buildStringNetwork      *Build gene network from peptide ids*

---

### Description

This can reduce the dimension of the original network, as there may not be a mapping between peptide and gene id

### Usage

```
buildStringNetwork(  
  stringTbl,  
  useNames = c("protein", "ensembl", "external"),  
  string.tbl = deprecated(),  
  use.names = deprecated()  
)
```

### Arguments

stringTbl	data.frame or tibble with colnames and rownames as ensembl peptide id ( <i>same order</i> ).
useNames	character(1) that defaults to use protein names <code>_('protein')</code> , other options are <code>'ensembl'</code> for ensembl gene id or <code>'external'</code> for external gene names.
string.tbl	<b>[Deprecated]</b>
use.names	<b>[Deprecated]</b>

### Value

a new matrix with gene ids instead of peptide ids. The size of matrix can be different as there may not be a mapping or a peptide mapping can have multiple genes.

### See Also

[stringDBhomoSapiens\(\)](#)

### Examples

```
interactions <- stringDBhomoSapiens(scoreThreshold = 100)  
string_network <- buildStringNetwork(interactions)  
  
# number of edges  
sum(string_network != 0)
```

---

cv.glmDegree	<i>Calculate cross validating GLM model with network-based regularization</i>
--------------	---

---

## Description

network parameter accepts:

## Usage

```
cv.glmDegree(  
  xdata,  
  ydata,  
  network,  
  options = networkOptions(),  
  experiment = NULL,  
  network.options = deprecated(),  
  experiment.name = deprecated(),  
  ...  
)
```

```
cv.glmHub(  
  xdata,  
  ydata,  
  network,  
  options = networkOptions(),  
  experiment = NULL,  
  network.options = deprecated(),  
  experiment.name = deprecated(),  
  ...  
)
```

```
cv.glmOrphan(  
  xdata,  
  ydata,  
  network,  
  options = networkOptions(),  
  experiment = NULL,  
  network.options = deprecated(),  
  experiment.name = deprecated(),  
  ...  
)
```

```
cv.glmSparseNet(  
  xdata,  
  ydata,  
  network,
```

```

options = networkOptions(),
experiment = NULL,
network.options = deprecated(),
experiment.name = deprecated(),
...
)

```

### Arguments

xdata	input data, can be a matrix or MultiAssayExperiment.
ydata	response data compatible with glmnet.
network	type of network, see below.
options	options to calculate network.
experiment	name of experiment to use as input in MultiAssayExperiment object (only if xdata is an object of this class).
network.options	<b>[Deprecated]</b>
experiment.name	<b>[Deprecated]</b>
...	parameters that <code>glmnet::cv.glmnet()</code> accepts.

### Details

- string to calculate network based on data (correlation, covariance)
- matrix representing the network
- vector with already calculated penalty weights (can also be used directly glmnet)

### Value

an object just as `cv.glmnet`

### Functions

- `cv.glmDegree()`: penalizes nodes with small degree (*inversion penalization*  $h(x) = 1 / x$ ).
- `cv.glmHub()`: penalizes nodes with small degree (*normalized heuristic that promotes nodes with many edges*).
- `cv.glmOrphan()`: penalizes nodes with high degree (*normalized heuristic that promotes nodes with few edges*).

### See Also

Model with the same penalizations `glmSparseNet()`.

**Examples**

```
# Degree penalization

xdata <- matrix(rnorm(100), ncol = 5)
cv.glmDegree(
  xdata,
  rnorm(nrow(xdata)),
  "correlation",
  family = "gaussian",
  nolds = 5,
  options = networkOptions(minDegree = .2)
)

# Hub penalization

xdata <- matrix(rnorm(100), ncol = 5)
cv.glmHub(
  xdata,
  rnorm(nrow(xdata)),
  "correlation",
  family = "gaussian",
  nolds = 5,
  options = networkOptions(minDegree = .2)
)

# Orphan penalization

xdata <- matrix(rnorm(100), ncol = 5)
cv.glmOrphan(
  xdata,
  rnorm(nrow(xdata)),
  "correlation",
  family = "gaussian",
  nolds = 5,
  options = networkOptions(minDegree = .2)
)

# Gaussian model
xdata <- matrix(rnorm(500), ncol = 5)
cv.glmSparseNet(
  xdata, rnorm(nrow(xdata)), "correlation",
  family = "gaussian"
)
cv.glmSparseNet(
  xdata, rnorm(nrow(xdata)), "covariance",
  family = "gaussian"
)

#
#
# Using MultiAssayExperiment with survival model
library(MultiAssayExperiment)
data("miniACC", package = "MultiAssayExperiment")
```

```

xdata <- miniACC

#
# build valid data with days of last follow up or to event
event.ix <- which(!is.na(xdata$days_to_death))
cens.ix <- which(!is.na(xdata$days_to_last_followup))
xdata$surv_event_time <- array(NA, nrow(colData(xdata)))
xdata$surv_event_time[event.ix] <- xdata$days_to_death[event.ix]
xdata$surv_event_time[cens.ix] <- xdata$days_to_last_followup[cens.ix]

#
# Keep only valid individuals
valid.ix <- as.vector(!is.na(xdata$surv_event_time) &
  !is.na(xdata$vital_status) &
  xdata$surv_event_time > 0)
xdata.valid <- xdata[, rownames(colData(xdata))[valid.ix]]
ydata.valid <- colData(xdata.valid)[, c("surv_event_time", "vital_status")]
colnames(ydata.valid) <- c("time", "status")

#
cv.glmSparseNet(
  xdata.valid,
  ydata.valid,
  nfolds = 5,
  family = "cox",
  network = "correlation",
  experiment = "RNASeq2GeneNorm"
)

```

---

degreeCor

*Calculate the degree of the correlation network based on xdata*


---

## Description

Calculate the degree of the correlation network based on xdata

## Usage

```

degreeCor(
  xdata,
  cutoff = 0,
  considerUnweighted = FALSE,
  forceRecalcDegree = FALSE,
  forceRecalcNetwork = FALSE,
  nCores = 1,
  ...,
  consider.unweighted = deprecated(),

```

```

    force.recalc.degree = deprecated(),
    force.recalc.network = deprecated(),
    n.cores = deprecated()
  )

```

### Arguments

`xdata` calculate correlation matrix on each column.

`cutoff` positive value that determines a cutoff value.

`considerUnweighted` consider all edges as 1 if they are greater than 0.

`forceRecalcDegree` force recalculation of penalty weights (but not the network), instead of going to cache.

`forceRecalcNetwork` force recalculation of network and penalty weights, instead of going to cache.

`nCores` number of cores to be used.

`...` extra parameters for `cor` function.

`consider.unweighted` **[Deprecated]**

`force.recalc.degree` **[Deprecated]**

`force.recalc.network` **[Deprecated]**

`n.cores` **[Deprecated]**

### Value

a vector of the degrees.

### Examples

```

n.col <- 6
xdata <- matrix(rnorm(n.col * 4), ncol = n.col)
degreeCor(xdata)
degreeCor(xdata, cutoff = .5)
degreeCor(xdata, cutoff = .5, considerUnweighted = TRUE)

```

---

degreeCov

*Calculate the degree of the covariance network based on xdata*

---

### Description

Calculate the degree of the covariance network based on xdata

**Usage**

```

degreeCov(
  xdata,
  cutoff = 0,
  considerUnweighted = FALSE,
  forceRecalcDegree = FALSE,
  forceRecalcNetwork = FALSE,
  nCores = 1,
  ...,
  consider.unweighted = deprecated(),
  force.recalc.degree = deprecated(),
  force.recalc.network = deprecated(),
  n.cores = deprecated()
)

```

**Arguments**

xdata	calculate correlation matrix on each column.
cutoff	positive value that determines a cutoff value.
considerUnweighted	consider all edges as 1 if they are greater than 0.
forceRecalcDegree	force recalculation of penalty weights (but not the network), instead of going to cache.
forceRecalcNetwork	force recalculation of network and penalty weights, instead of going to cache.
nCores	number of cores to be used.
...	extra parameters for cov function.
consider.unweighted	<b>[Deprecated]</b>
force.recalc.degree	<b>[Deprecated]</b>
force.recalc.network	<b>[Deprecated]</b>
n.cores	<b>[Deprecated]</b>

**Value**

a vector of the degrees

**Examples**

```

n.col <- 6
xdata <- matrix(rnorm(n.col * 4), ncol = n.col)
degreeCov(xdata)
degreeCov(xdata, cutoff = .5)
degreeCov(xdata, cutoff = .5, considerUnweighted = TRUE)

```

---

downloadFileLocal	<i>Download files to local temporary path</i>
-------------------	---

---

**Description**

In case of new call it uses the temporary cache instead of downloading again.

**Usage**

```
downloadFileLocal(urlStr, oD = tempdir())
```

**Arguments**

urlStr	url of file to download
oD	temporary directory to store file

**Details**

Inspired by STRINGdb Bioconductor package, but using curl as file may be too big to handle.

**Value**

path to file

**Examples**

```
glmSparseNet::downloadFileLocal(  
  "https://string-db.org/api/tsv-no-header/version"  
)
```

---

ensemblGeneNames	<i>Retrieve ensembl gene names from biomaRt</i>
------------------	---

---

**Description**

Retrieve ensembl gene names from biomaRt

**Usage**

```
ensemblGeneNames(  
  geneId,  
  useCache = TRUE,  
  verbose = FALSE,  
  gene.id = deprecated(),  
  use.cache = deprecated()  
)
```

**Arguments**

geneId	character vector with gene names
useCache	Boolean indicating if biomaRt cache should be used
verbose	When using biomaRt in webservice mode and setting verbose to TRUE, the XML query to the webservice will be printed.
gene.id	<b>[Deprecated]</b>
use.cache	<b>[Deprecated]</b>

**Value**

a dataframe with external gene names, `ensembl_id`

**Examples**

```
ensemblGeneNames(c("MOB1A", "RFLNB", "SPIC", "TP53"))
```

---

geneNames	<i>Retrieve gene names from biomaRt</i>
-----------	---

---

**Description**

Retrieve gene names from biomaRt

**Usage**

```
geneNames(
  ensemblGenes,
  useCache = TRUE,
  verbose = FALSE,
  ensembl.genes = deprecated(),
  use.cache = deprecated()
)
```

**Arguments**

ensemblGenes	character vector with gene names in <code>ensembl_id</code> format
useCache	Boolean indicating if biomaRt cache should be used
verbose	When using biomaRt in webservice mode and setting verbose to TRUE, the XML query to the webservice will be printed.
ensembl.genes	<b>[Deprecated]</b>
use.cache	<b>[Deprecated]</b>

**Value**

a dataframe with external gene names, `ensembl_id`

**Examples**

```
geneNames(c("ENSG00000114978", "ENSG00000166211", "ENSG00000183688"))
```

---

glmSparseNet

*Calculate GLM model with network-based regularization*

---

**Description**

network parameter accepts:

- string to calculate network based on data (correlation, covariance)
- matrix representing the network
- vector with already calculated penalty weights (can also be used directly with glmnet)

**Usage**

```
glmSparseNet(  
  xdata,  
  ydata,  
  network,  
  options = networkOptions(),  
  experiment = NULL,  
  network.options = deprecated(),  
  experiment.name = deprecated(),  
  ...  
)
```

```
glmDegree(  
  xdata,  
  ydata,  
  network,  
  options = networkOptions(),  
  experiment = NULL,  
  network.options = deprecated(),  
  experiment.name = deprecated(),  
  ...  
)
```

```
glmHub(  
  xdata,  
  ydata,  
  network,  
  options = networkOptions(),  
  experiment = NULL,  
  network.options = deprecated(),  
  experiment.name = deprecated(),  
  ...  
)
```

```

    ...
  )

glmOrphan(
  xdata,
  ydata,
  network,
  options = networkOptions(),
  experiment = NULL,
  network.options = deprecated(),
  experiment.name = deprecated(),
  ...
)

```

### Arguments

xdata	input data, can be a matrix or MultiAssayExperiment.
ydata	response data compatible with glmnet.
network	type of network, see below.
options	options to calculate network.
experiment	name of experiment to use as input in MultiAssayExperiment object (only if xdata is an object of this class).
network.options	<b>[Deprecated]</b>
experiment.name	<b>[Deprecated]</b>
...	parameters that <code>glmnet::glmnet()</code> accepts.

### Value

an object just as glmnet

### Functions

- `glmDegree()`: penalizes nodes with small degree (*inversion penalization*  $h(x) = 1 / x$ ).
- `glmHub()`: Penalizes nodes with small degree (*normalized heuristic that promotes nodes with many edges*).
- `glmOrphan()`: Penalizes nodes with high degree (*normalized heuristic that promotes nodes with few edges*).

### See Also

Cross-validation functions `cv.glmSparseNet()`.

**Examples**

```

xdata <- matrix(rnorm(100), ncol = 20)
glmSparseNet(xdata, rnorm(nrow(xdata)), "correlation", family = "gaussian")
glmSparseNet(xdata, rnorm(nrow(xdata)), "covariance", family = "gaussian")

#
#
# Using MultiAssayExperiment
# load data
library(MultiAssayExperiment)
data("miniACC", package = "MultiAssayExperiment")

xdata <- miniACC
# TODO taking out x individuals missing values
# build valid data with days of last follow up or to event
event.ix <- which(!is.na(xdata$days_to_death))
cens.ix <- which(!is.na(xdata$days_to_last_followup))

xdata$surv_event_time <- array(NA, nrow(colData(xdata)))
xdata$surv_event_time[event.ix] <- xdata$days_to_death[event.ix]
xdata$surv_event_time[cens.ix] <- xdata$days_to_last_followup[cens.ix]

# Keep only valid individuals
valid.ix <- as.vector(!is.na(xdata$surv_event_time) &
  !is.na(xdata$vital_status) &
  xdata$surv_event_time > 0)
xdata.valid <- xdata[, rownames(colData(xdata))[valid.ix]]
ydata.valid <- colData(xdata.valid)[, c("surv_event_time", "vital_status")]
colnames(ydata.valid) <- c("time", "status")

glmSparseNet(
  xdata.valid,
  ydata.valid,
  family = "cox",
  network = "correlation",
  experiment = "RNASeq2GeneNorm"
)

# Degree penalization

xdata <- matrix(rnorm(100), ncol = 5)
glmDegree(
  xdata,
  rnorm(nrow(xdata)),
  "correlation",
  family = "gaussian",
  options = networkOptions(minDegree = .2)
)

xdata <- matrix(rnorm(100), ncol = 5)
glmHub(
  xdata,

```

```

    rnorm(nrow(xdata)),
    "correlation",
    family = "gaussian",
    options = networkOptions(minDegree = .2)
  )
  # Orphan penalization

xdata <- matrix(rnorm(100), ncol = 5)
glmOrphan(
  xdata,
  rnorm(nrow(xdata)),
  "correlation",
  family = "gaussian",
  options = networkOptions(minDegree = .2)
)

```

---

hallmarks

*Retrieve hallmarks of cancer count for genes*


---

### Description

**[Defunct]** The API has been removed and this function is no longer available.

### Usage

```

hallmarks(
  genes,
  metric = "count",
  hierarchy = "full",
  generate.plot = TRUE,
  show.message = FALSE
)

```

### Arguments

genes	gene names
metric	see below
hierarchy	see below
generate.plot	flag to indicate if return object has a ggplot2 object
show.message	flag to indicate if run_cache method shows messages

### Value

data.frame with choosen metric and hierarchy It also returns a vector with genes that do not have any hallmarks.

See <http://chat.lionproject.net/api> for more details on the metric and hallmarks parameters

To standardize the colors in the gradient you can use `scale_fill_gradientn(limits=c(0,1), colours=topo.colors(3))` to limit between 0 and 1 for cprob and -1 and 1 for npmi

---

heuristicScale	<i>Heuristic function to use in high dimensions</i>
----------------	---

---

### Description

Heuristic function to use in high dimensions

### Usage

```
heuristicScale(  
  x,  
  subExp10 = -1,  
  expMult = -1,  
  subExp = -1,  
  sub.exp10 = deprecated(),  
  exp.mult = deprecated(),  
  sub.exp = deprecated()  
)
```

### Arguments

x	vector of values to scale
subExp10	value to subtract to base 10 exponential, for example: $10^{\theta - \text{subExp10}} = 10^{\theta - \text{subExp10}}$
expMult	parameter to multiply exponential, i.e. to have a negative exponential or positive
subExp	value to subtract for exponential, for example if $x = 0$ , $\exp(\theta) - \text{sub.exp} = 1 - \text{sub.exp}$
sub.exp10	<b>[Deprecated]</b>
exp.mult	<b>[Deprecated]</b>
sub.exp	<b>[Deprecated]</b>

### Value

a vector of scaled values

### Examples

```
heuristicScale(rnorm(1:10))
```

hubHeuristic                    *Heuristic function to penalize nodes with low degree*

---

**Description**

Heuristic function to penalize nodes with low degree

**Usage**

```
hubHeuristic(x)
```

**Arguments**

x                    single value of vector

**Value**

transformed

**Examples**

```
hubHeuristic(rnorm(1:10))
```

---

myColors                    *Custom pallete of colors*

---

**Description**

Custom pallete of colors

**Usage**

```
myColors(ix = NULL)

# deprecated, please use myColors()
my.colors(ix = NULL)
```

**Arguments**

ix                    index for a color

**Value**

a color

**Examples**

```
myColors()
myColors(5)
```

---

mySymbols	<i>Custom palette of symbols in plots</i>
-----------	---

---

**Description**

Custom palette of symbols in plots

**Usage**

```
mySymbols(ix = NULL)

# deprecated, please use mySymbols()
my.symbols(ix = NULL)
```

**Arguments**

ix                    index for symbol

**Value**

a symbol

**Examples**

```
mySymbols()
mySymbols(2)
```

---

networkCorParallel	<i>Calculates the correlation network</i>
--------------------	---

---

**Description**

Calculates the correlation network

**Usage**

```
networkCorParallel(
  xdata,
  buildOutput = "matrix",
  nCores = 1,
  forceRecalcNetwork = FALSE,
  showMessage = FALSE,
  ...,
  build.output = deprecated(),
  n.cores = deprecated(),
  force.recalc.network = deprecated(),
  show.message = deprecated()
)
```

**Arguments**

xdata	base data to calculate network
buildOutput	if output returns a 'matrix', 'vector' of the upper triu without the diagonal or NULL with any other argument
nCores	number of cores to be used
forceRecalcNetwork	force recalculation, instead of going to cache
showMessage	shows cache operation messages
...	extra parameters for fun
build.output	lifecycle::badge("deprecated") without the diagonal or NULL with any other argument
n.cores	lifecycle::badge("deprecated")
force.recalc.network	lifecycle::badge("deprecated")
show.message	lifecycle::badge("deprecated")

**Value**

depends on build.output parameter

**Examples**

```
n_col <- 6
xdata <- matrix(rnorm(n_col * 4), ncol = n_col)
networkCorParallel(xdata)
```

---

networkCovParallel     *Calculates the covariance network*

---

**Description**

Calculates the covariance network

**Usage**

```
networkCovParallel(
  xdata,
  buildOutput = "matrix",
  nCores = 1,
  forceRecalcNetwork = FALSE,
  showMessage = FALSE,
  ...,
  build.output = deprecated(),
  n.cores = deprecated(),
  force.recalc.network = deprecated(),
  show.message = deprecated()
)
```

**Arguments**

xdata	base data to calculate network
buildOutput	if output returns a 'matrix', 'vector' of the upper triu without the diagonal or NULL with any other argument
nCores	number of cores to be used
forceRecalcNetwork	force recalculation, instead of going to cache
showMessage	shows cache operation messages
...	extra parameters for fun
build.output	lifecycle::badge("deprecated") without the diagonal or NULL with any other argument
n.cores	lifecycle::badge("deprecated")
force.recalc.network	lifecycle::badge("deprecated")
show.message	lifecycle::badge("deprecated")

**Value**

depends on build.output parameter

**Examples**

```
n.col <- 6
xdata <- matrix(rnorm(n.col * 4), ncol = n.col)
networkCovParallel(xdata)
```

---

networkOptions	<i>Setup network options</i>
----------------	------------------------------

---

**Description**

Setup network options, such as using weighted or unweighted degree, which centrality measure to use

**Usage**

```
networkOptions(
  method = "pearson",
  unweighted = TRUE,
  cutoff = 0,
  centrality = "degree",
  minDegree = 0,
  nCores = 1,
  transFun = function(x) x,
  min.degree = deprecated(),
```

```
n.cores = deprecated(),
trans.fun = deprecated()
)
```

### Arguments

method	in case of correlation and covariance, which method to use.
unweighted	calculate degree using unweighted network.
cutoff	cutoff value in network edges to trim the network.
centrality	centrality measure to use, currently only supports degree.
minDegree	minimum value that individual penalty weight can take.
nCores	number of cores to use, default to 1.
transFun	See details below.
min.degree	<b>[Deprecated]</b>
n.cores	<b>[Deprecated]</b>
trans.fun	<b>[Deprecated]</b>

The transFun argument takes a function definition that will apply a transformation to the penalty vector calculated from the degree. This transformation allows to change how the penalty is applied.

### Value

a list of options

### See Also

[glmOrphan\(\)](#) and [glmDegree\(\)](#)

### Examples

```
networkOptions(unweighted = FALSE)
```

---

orphanHeuristic	<i>Heuristic function to penalize nodes with high degree</i>
-----------------	--

---

### Description

Heuristic function to penalize nodes with high degree

### Usage

```
orphanHeuristic(x)
```

### Arguments

x	single value of vector
---	------------------------

**Value**

transformed

**Examples**

```
orphanHeuristic(rnorm(1:10))
```

---

protein2EnsemblGeneNames

*Retrieve ensembl gene ids from proteins*

---

**Description**

Retrieve ensembl gene ids from proteins

**Usage**

```
protein2EnsemblGeneNames(  
  ensemblProteins,  
  useCache = TRUE,  
  verbose = FALSE,  
  ensembl.proteins = deprecated(),  
  use.cache = deprecated()  
)
```

**Arguments**

ensemblProteins	character vector with gene names in ensembl_peptide_id format
useCache	Boolean indicating if biomaRt cache should be used
verbose	When using biomaRt in webservice mode and setting verbose to TRUE, the XML query to the webservice will be printed.
ensembl.proteins	<b>[Deprecated]</b>
use.cache	<b>[Deprecated]</b>

**Value**

a dataframe with external gene names, ensembl\_peptide\_id

**Examples**

```
protein2EnsemblGeneNames(c(  
  "ENSP00000235382",  
  "ENSP00000233944",  
  "ENSP00000216911"  
)
```

---

separate2GroupsCox      *Separate data in High and Low risk groups (based on Cox model)*

---

### Description

Draws multiple kaplan meyer survival curves (or just 1) and calculates logrank test

### Usage

```
separate2GroupsCox(
  chosenBetas,
  xdata,
  ydata,
  probs = c(0.5, 0.5),
  noPlot = FALSE,
  plotTitle = "SurvivalCurves",
  xlim = NULL,
  ylim = NULL,
  expandYZero = FALSE,
  legendOutside = FALSE,
  stopWhenOverlap = TRUE,
  ...,
  chosen.betas = deprecated(),
  no.plot = deprecated(),
  plot.title = deprecated(),
  expand.yzero = deprecated(),
  legend.outside = deprecated(),
  stop.when.overlap = deprecated()
)
```

### Arguments

chosenBetas	list of testing coefficients to calculate prognostic indexes, for example <code>list(Age = some_vector)</code> .
xdata	n x m matrix with n observations and m variables.
ydata	Survival object.
probs	How to separate high and low risk patients 50%-50% is the default, but for top and bottom 40% -> <code>c(.4, .6)</code> .
noPlot	Only calculate p-value and do not generate survival curve plot.
plotTitle	Name of file if.
xlim	Optional argument to limit the x-axis view.
ylim	Optional argument to limit the y-axis view.
expandYZero	expand to y = 0.
legendOutside	If TRUE legend will be outside plot, otherwise inside.

```

stopWhenOverlap      when probs vector allows for overlapping of samples in both groups, then stop.
...                  additional parameters to survminer::ggsurvplot
chosen.btas          [Deprecated]
no.plot              [Deprecated]
plot.title           [Deprecated]
expand.yzero         [Deprecated]
legend.outside       [Deprecated]
stop.when.overlap    [Deprecated]
                    Otherwise it will calculate with duplicate samples, i.e. simply adding them to
                    xdata and ydata (in a different group).

```

**Value**

object with logrank test and kaplan-meier survival plot

A list with plot, p-value and kaplan-meier object. The plot was drawn from `survminer::ggsurvplot` with only the palette, data and fit arguments being defined and keeping all other defaults that can be customized as additional parameters to this function.

**See Also**

[survminer::ggsurvplot\(\)](#)

**Examples**

```

xdata <- survival::ovarian[, c("age", "resid.ds")]
ydata <- data.frame(
  time = survival::ovarian$futime,
  status = survival::ovarian$fustat
)
separate2GroupsCox(c(age = 1, 0), xdata, ydata)
separate2GroupsCox(c(age = 1, 0.5), xdata, ydata)
separate2GroupsCox(
  c(age = 1), c(1, 0, 1, 0, 1, 0),
  data.frame(time = runif(6), status = rbinom(6, 1, .5))
)
separate2GroupsCox(list(
  aa = c(age = 1, 0.5),
  bb = c(age = 0, 1.5)
), xdata, ydata)

```

---

```
string.network.700.cache
```

*Cache of protein-protein network, as it takes some time to retrieve and process this will facilitate the vignette building*

---

### Description

It was filtered with combined\_scores and individual scores below 700 without text-based scores

### Usage

```
data('string.network.700.cache', package = 'glmSparseNet')
```

### Format

An object of class dgCMatix with 11033 rows and 11033 columns.

### References

<https://string-db.org/>

---

```
stringDBhomoSapiens Download protein-protein interactions from STRING DB
```

---

### Description

Download protein-protein interactions from STRING DB

### Usage

```
stringDBhomoSapiens(
  version = "11.0",
  scoreThreshold = 0,
  removeText = TRUE,
  score_threshold = deprecated(),
  remove.text = deprecated()
)
```

### Arguments

version	version of the database to use
scoreThreshold	remove scores below threshold
removeText	remove text mining-based scores
score_threshold	<b>[Deprecated]</b>
remove.text	<b>[Deprecated]</b>

**Value**

a data.frame with rows representing an interaction between two proteins, and columns the count of scores above the given `score_threshold`

**Examples**

```
stringDBhomoSapiens(scoreThreshold = 800)
```

# Index

- \* **data**
  - string.network.700.cache, [42](#)
- \* **internal**
  - .glmSparseNetPrivate, [12](#)
  - glmSparseNet-package, [3](#)
- .baseDir, [4](#)
- .biomartLoad, [4](#)
- .buildFunctionDigest, [5](#)
- .cacheCompression, [6](#)
- .calcPenalty, [7](#)
- .calculateResult, [7](#)
- .combinedScore, [8](#)
- .createDirectoryForCache, [9](#)
- .curlWorkaround, [9](#)
- .degreeGeneric, [10](#)
- .digestCache, [11](#)
- .glmSparseNetPrivate, [12](#)
- .networkGenericParallel, [13](#)
- .networkWorker, [14](#)
- .runCache, [14](#)
- .runCache, function-method (.runCache), [14](#)
- .saveRunCache, [16](#)
- .showMessage, [16](#)
- .tempdirCache, [17](#)
- .writeReadme, [17](#)
  
- balanced.cv.folds (balancedCvFolds), [18](#)
- balancedCvFolds, [18](#)
- buildLambda, [18](#)
- buildStringNetwork, [20](#)
  
- cv.glmDegree, [21](#)
- cv.glmHub (cv.glmDegree), [21](#)
- cv.glmOrphan (cv.glmDegree), [21](#)
- cv.glmSparseNet (cv.glmDegree), [21](#)
- cv.glmSparseNet(), [30](#)
  
- degreeCor, [24](#)
- degreeCov, [25](#)
  
- downloadFileLocal, [27](#)
  
- ensemblGeneNames, [27](#)
  
- geneNames, [28](#)
- glmDegree (glmSparseNet), [29](#)
- glmDegree(), [38](#)
- glmHub (glmSparseNet), [29](#)
- glmnet::cv.glmnet(), [22](#)
- glmnet::glmnet(), [30](#)
- glmOrphan (glmSparseNet), [29](#)
- glmOrphan(), [38](#)
- glmSparseNet, [29](#)
- glmSparseNet(), [22](#)
- glmSparseNet-package, [3](#)
  
- hallmarks, [32](#)
- heuristicScale, [33](#)
- hubHeuristic, [34](#)
  
- my.colors (myColors), [34](#)
- my.symbols (mySymbols), [35](#)
- myColors, [34](#)
- mySymbols, [35](#)
  
- networkCorParallel, [35](#)
- networkCovParallel, [36](#)
- networkOptions, [37](#)
  
- orphanHeuristic, [38](#)
  
- protein2EnsemblGeneNames, [39](#)
  
- separate2GroupsCox, [40](#)
- string.network.700.cache, [42](#)
- stringDBhomoSapiens, [42](#)
- stringDBhomoSapiens(), [20](#)
- survminer::ggsurvplot(), [41](#)